REMARKS

Reconsideration of this application is respectfully requested. Claims 69-71 have been cancelled by way of this amendment, without prejudice or disclaimer. Claims 98-100 have been added by way of this amendment. Claims 55-57, 59-68, 72-77, and 79-100 are pending in the application upon entry of this amendment.

Claims 55-57, 59-63, 67, 75-77, 79-87, 90-91, 93-97 have been amended to recite "rat" rather than "non-human mammal." Support for this amendment can be found in the claims as originally filed (see, *e.g.*, claims 41-43, 49 and 54 of the Preliminary Amendment filed with the application on November 20, 2000 and originally filed claim 8 of the parent application (U.S.S.N. 08/994,689)) and throughout the specification, for example, on page 5, lines 4-14; page 11, lines 4-5; and page 22, line 16- page 23 line 12.

Claims 55, 63-65, 75, 80, and 81 have been amended to recite "chondrocyte-specific promoter", rather than "joint-specific promoter." Support for this amendment can be found in the claims as originally filed (see, *e.g.*, claims 28, 39, 41 and 42 of the Preliminary Amendment filed with the application on November 20, 2000) and throughout the specification, for example, on page 37, line 1; page 6, lines 4-5; and page 13, lines 3-4.

Applicants' representative Heather Morehouse Ettinger thanks Examiner Wilson for discussing amendments to claims 90-96 very similar to those presented herewith by telephone with her and for reviewing those amendments by way of an informal facsimile communication on February 1, 2005. Upon review, the Examiner indicated by way of a telephone call to Dr. Ettinger that amendments similar to those presented herewith would obviate the indefiniteness rejections and that he would enter those amendments.

The amendments presented herewith differ from those presented to Examiner Wilson informally on February 1 only by putting the phrase "expression of the metalloproteinase results in" in a part of step (b) of the claims, which is more grammatically correct.

Applicants' representative Van Nguyen thanks Examiner Wilson for discussing the amendments to claims 90-96 presented in the previously presented but not entered Response and

Amendment filed on February 2, 2005. During this informal communication, Examiner Wilson indicated that the claim language presented on February 1 would be deemed acceptable.

Claims 90-96 have been amended in order to obviate the Examiner's rejections of these claims for alleged indefiniteness. Support for these amendments can be found in the specification, for example, at page 7, line 15 to page 8, line 3; and page 21, line 1 to page 22, line 9.

Support for new claims 98-100 can be found throughout the specification (see, *e.g.*, page 20, line 13- page 21, line 2) and in the claims as originally filed (see, *e.g.*, claims 52-54 of the Preliminary Amendment filed with the application on November 20, 2000 and in original claims 25-27 of the parent application).

No new matter has been added by way of these claim amendments or new claims.

Information Disclosure Statement

Applicants thank the Examiner for acknowledging consideration of the Information Disclosure Statement filed on August 9, 2004.

Rejections under 35 U.S.C. § 112, first paragraph- written description

Claims 55-57, 59-77, and 79-97 have been rejected for alleged failure to fulfill the written description requirement. Specifically, the Examiner has rejected these claims because the specification allegedly does not disclose any promoters that meet the description of "joint-specific promoters" other than the type II collagen promoter.[1]

By way of the instant amendment, the phrase "joint-specific promoter" has been replaced with the phrase "chondrocyte-specific promoter." The Examiner has previously rejected claims with a similar phrase ("chondrocyte tissue-specific promoter") for alleged lack of written description

[1] Although previous Actions have rejected "transgenic non-human mammals" for alleged failure to meet the written description requirement, the present Action does not present this rejection. Accordingly, it is presumed withdrawn.

(see, *e.g.*, Final Office Action mailed April 9, 2003 in connection with this application). Accordingly, Applicants provide the following discussion.

There is an extensive description of promoters that direct transcription in joint tissues, such as chondrocyte-specific promoters, *i.e.*, that provide spatial control of expression, on page 15, line 19 to page 16, line 6 of the specification. The specification clearly discloses that expression of a matrix decoding enzyme (MDE) in chondrocytes, which are the cells found in joints, results in localized degradation of extracellular matrix proteins. Having established this principle with a working example (the Type II collagen promoter), one of ordinary skill in the art would recognize that joint (*i.e.*, chondrocyte)-specific expression of an MDE, particularly a collagen II-degrading MMP, would yield the desired joint degradation.[2]

The thrust of rejections of claims containing the "chondrocyte tissue-specific promoter" or "chondrocyte-specific promoter" limitation is misplaced: the claimed invention is a specific type of transgenic mammals (rats) and methods of using these mammals (rats and mice). The Examiner did not argue that there is an inadequate written description of the claimed invention as a whole. Instead, the Examiner focused on one element of the invention, a tissue-specific promoter, and generated a rejection of the claims based on the supposed lack of written description of that single element.

The specification sets forth a generic written description of the claimed transgenic mammals, of which chondrocyte-specific regulated expression is an important component. This one component of the invention, which, in context of the invention, operates like a specific part of a machine to achieve a mammal as claimed. Applicants have more than adequately satisfied the written description requirement by providing an explicit description in words of this generic invention, and through examples of the invention's ability to degrade collagen in both spatial (joint) and temporal (inducible) regulation in an animal. ("Coordinated spatial and temporal control of

[2] This claim does not "preempt the future before it has arrived" as feared by the Examiner (see January 30, 2002 Office Action, page 5, citing *Fiers v. Revel* and *Regents of the University of California v. Eli Lilly*). The future -- other chondrocyte-specific promoters -- is free to arrive unhindered. However, claims of proper scope preserve to the inventors the full measure of their invention, which includes use of any such "future" chondrocyte-specific promoters to generate the claimed transgenic animal.

MDE expression is preferably achieved by (i) placing expression of the repressor-activator fusion polypeptide or the transcriptional activator polypeptide under the control of a joint-specific promoter; (ii) placing the expression of the MDE or a derivative thereof under the control of a promoter responsive to the repressor-activator fusion polypeptide or the transcriptional activator polypeptide; and (iii) maintaining the transgenic animal during fetal development and early life under conditions in which MDE expression is repressed." See page 16, lines 7-13).

That the concept of chondrocyte-specific promoters was well-known in the art at the time of invention is demonstrated in the annexed Declaration of Dr. Roger Askew under 37 C.F.R. § 1.132 ("the Askew Declaration" (see paragraph 8 Askew Declaration). One reference, dating from 1997, described in and accompanying the Askew Declaration (Pirok *et al.*, Structural and Functional Analysis of the Chick Chondroitin Sulfate Proteoglycan (Aggrecan) Promoter and Enhancer Region. *The Journal of Biological Chemistry*. Vol. 272, No. 17, pp. 11566-11574, 1997; attached as Exhibit B) discloses mapping of 5' segments (enhancer and silencer, *i.e.* promoter, elements) of a cartilage-specific gene: the chondroitin sulfate proteoglycan (CSPG; Aggrecan) gene. These promoter elements are responsible for the chondrocyte-specific expression of the CSPG gene. Another reference, which was received by the journal in which it is published in May 1998 and thus represents work done in 1997, described in and accompanying the Askew Declaration (see paragraph 8), (Lefebvre *et al.*, A New Long Form of Sox5 (L-Sox5), Sox6 and Sox9 are coexpressed in chondrogenesis and cooperatively activate the type II collagen gene, *The Embo Journal*. Vol. 17, No. 19, pp. 5718-5733, 1998; "Lefebvre"; attached as Exhibit C), discloses cooperation of transcription factors Sox5 and Sox6 in providing chondrocyte-specific expression of the *Col2a1* gene. Specifically, this reference describes the elements of at least two promoters, the *Col2a1* and *Col11a2* promoters, which lead to chondrocyte-specific gene expression (see, e.g., p. 5719, col. 1 first and second full paragraphs of Lefebvre). Accordingly, not only do these references describe chondrocyte-specific promoters known in the art at the time of the invention, but they also describe the characterization of the molecular features of these promoters. In conclusion, both of the references described chondrocyte-specific promoters known in the art at the time of the present invention.

That chondrocyte-specific promoters, wherein chondrocytes are cells that make up cartilage tissue, was well-known in the art at the time of invention is also demonstrated in the Second Neuhold Declaration (a copy of the Second Neuhold Declaration and its accompanying Exhibits (Tabs 1-9), which were originally filed in the parent case U.S.S.N. 08/994,689 on August 31, 2000, was filed as Exhibit 5 with the April 30, 2002 Amendment and Response in the instant application). As set forth in the Second Neuhold Declaration (paragraph 7) the specific promoter employed to achieve tissue-specific expression does not make any difference, as one of ordinary skill in the art would readily appreciate. A number of issued patents that cover transgenic animals establish that claims reciting generic tissue-specific expression of a transgene do not offend the written description requirement, because the actual tissue specific promoter is usually of no moment. See for example U.S. Patent Nos. 5,625,124 (claim 1: "gut epithelial cell specific promoter"); 5,880,327 (claim 1: "a mammary-gland specific promoter"); 5,917,123 (claim 1: "a cardiac-specific regulatory region"); and 6,028,245 (claim 1: "a promoter that drives expression of the transgene in skin") (all attached as Exhibit 8 with the April 30, 2002 Amendment and Response in the instant application).

Accordingly, chondrocyte-specific promoters are adequately described by the specification.

New matter

The Examiner has previously rejected the phrase "chondrocyte tissue-specific promoter" for allegedly being new matter (see, *e.g.*, Final Office Action mailed April 9, 2003 in connection with this application). Accordingly, Applicants provide the following discussion.

Applicants respectfully submit that the phrase "chondrocyte tissue-specific promoter" or "chondrocyte-specific promoter" is not new matter. Applicants assert that support for the phrase appears in page 37, line 1, which discusses "tissue-specific expression conferred by the type II collagen promoter." At page 6, lines 4-5, the specification states that "... the recombinant MDE-encoding genes are selectively expressed in articular chondrocytes...;" likewise, at page 13, lines 3-4, "...MMP activity is selectively expressed in joint tissues, most preferably in articular chondrocytes." One of ordinary skill in the art would readily appreciate that the inventors had possession of a transgenic mammal with chondrocyte-specific expression of the transgene from this

description. The Examiner's previous new matter rejection failed to consider these express teachings in the specification. Accordingly, the phrase "chondrocyte-specific promoter" does not constitute new matter.

Rejections under 35 U.S.C. § 112, first paragraph- enablement

Joint-specific promoters

Claims 54-57, 59-77, and 79-97 have been rejected for alleged failure to fulfill the enablement requirement because the specification allegedly does not provide enablement for any "joint-specific promoter" as previously claimed.

By way of the instant amendment, the phrase "joint-specific promoter" has been replaced with the phrase "chondrocyte-specific promoter." The Examiner has previously rejected claims with this phrase for alleged lack of enablement (see, *e.g.*, Final Office Action mailed April 9, 2003 in connection with this application). Accordingly, Applicants provide the following discussion.

The Examiner has previously asserted that the specification does not enable any chondrocyte tissue-specific promoter. Thus, the Examiner concludes that the claims should be limited to a Type II collagen promoter to regulate expression of the regulator polypeptide. Applicants cannot agree with this rejection, as it unduly limits the claims. The claims, after all, are directed to a particular type of transgenic mammal, which successfully employs, but is not necessarily limited to, a Type II collagen-specific promoter.

The disclosure and examples show that one can practice the claimed invention (a transgenic mammal capable of degrading collagen primarily or exclusively in the joints of a temporally controlled fashion) using any chondrocyte-specific promoter. As outlined above, in the discussion of the rejection under 35 U.S.C. § 112, first paragraph – written description, there is support in the specification for chondrocyte-specific promoters. In the context of the entire invention, expression of MDEs are necessarily joint (*i.e.* chondrocyte)-specific; otherwise, the transgenic mammals would suffer from non-specific, systemic degradation of collagen throughout the body. See page 4, line 14 - page 5, line 3 (constitutive expression of MDEs causes embryonic lethality). Given the

importance of tissue-specific expression of the transgene to the invention and the ease with which one of ordinary skill can substitute one promoter for another, it is well within the level of skill for one in the art to use any chondrocyte-specific promoter in this invention, whether known or yet to be discovered, to limit expression of the MDEs to the transgenic animal's joints. As discussed above, the concept of tissue-specific promoters, such as the cartilage tissue chondrocyte-specific promoters instantly claimed, was well-known in the art at the time of invention. In other words, as disclosed in the application, tissue-specific expression is very important, but the exact tissue-specific promoter used to achieve it matters very little.

As set forth in the previously filed Second Neuhold Declaration (at paragraph 7), the specific promoter employed to achieve tissue specific expression does not make any difference, as one of ordinary skill in the art would readily appreciate. A number of issued patents that cover transgenic animals establish that tissue-specific expression is sufficiently enabled for expression of a transgene, because the actual tissue specific promoter is usually of no moment. Moreover, it is proper in a patent for a transgenic animal to claim the promoter by virtue of its tissue specificity rather than identity. *See* U.S. Patent Nos. 5,625,124 (claim 1: "gut epithelial cell specific promoter"); 5,880,327 (claim 1: "a mammary-gland specific promoter"); 5,917,123 (claim 1: "a cardiac-specific regulatory region"); 6,028,245 (claim 1: "a promoter that drives expression of the transgene in skin") (all attached as Exhibit 8). Again, Applicants request the Examiner to examine the invention as a whole.

The specification adequately discloses a method for making and using the present invention; disclosing other methods by which the claimed invention may be made is not necessary. See *Spectra-Physics, Inc. v. Coherent, Inc.*, 827 F.2d 1524, 1533, 3 USPQ2d 1737, 1743 (Fed. Cir. 1987). Because chondrocyte-specific promoters were known in the art at the time of invention (see, *e.g.*, Askew Declaration, paragraph 8) it is not required to specify other chondrocyte-specific promoters that may be used in the method disclosed in the present invention. The chondrocyte-specific promoter is a single element in the claimed method, and given that chondrocyte-specific promoters are well known in the art, cannot be viewed in isolation to justify an enablement rejection.

Furthermore, Applicants are not required to enable any chondrocyte-specific promoters that arise *after* the date of filing. The Court of Appeals for the Federal Circuit has recently stated that the "law does not expect an applicant to disclose knowledge invented or developed after the filing date." *Chiron Corp. v. Genentech, Inc.*, 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1326 (Fed. Cir. 2004) (holding that, despite the lack of specific reference to chimeric antibodies in the specification, the enablement requirement was satisfied with regard to chimeric antibodies because chimeric antibody technology did not arise until after the application was filed). Technology arising after the filing date is "by definition, outside the bounds of the enablement requirement," and is enabled by the specification provided that the generic description in the specification encompasses the new technology. *Id.* Applicants have met their burden of enabling the genus of chondrocyte-specific promoters by adequately enabling Type II collagen promoters, and the generic description is broad enough to cover any chondrocyte-specific promoters arising after the filing date. See page 15, line 19 - page 16, line 6. Thus, Applicants are not required to enable any chondrocyte-specific promoters identified after the application was filed.

Lastly, as set forth in the annexed Askew Declaration (paragraph 11) and in the previously filed first Neuhold Declaration, it would be routine for one of ordinary skill in the art to identify the promoter(s) responsible for chondrocyte-specific expression. For example, simple β-galactosidase expression experiments would demonstrate whether a promoter were a chondrocyte-specific promoter (see, *e.g.*, first Neuhold Declaration).

In short, rejecting claims reciting "chondrocyte-specific promoters" is in error given the advanced state of the art, including general recognition of enablement of creation of transgenic animals (irrespective of whether or not such efforts are cost effective), widespread knowledge of regulatable expression systems, the understanding in the art of tissue-specific expression, and the number of well known extracellular matrix degrading enzymes from which to choose. The present invention is broadly enabled.

Non-human mammals

Claims 54-57, 59-77, and 79-97 have been rejected for alleged failure to fulfill the enablement requirement because the specification allegedly does not provide enablement for any "non-human mammal" as previously claimed.

By way of the instant amendment, the phrase "non-human mammal" has been replaced with "rat." The Examiner has previously rejected claims with this phrase for alleged lack of enablement (see, *e.g.*, Final Office Action mailed April 9, 2003 in connection with this application). Accordingly, Applicants provide the following discussion.

Transgenic nonhuman mammals, particularly mice and rats, were known and prepared routinely by ordinary research scientists at the time this invention was made. It is also a known and accepted that, as with every other experimental system in biology such as cloning and hydridomas, not every transgenic embryo will yield a transgenic animal with the desired characteristics, but that routine screening and selection techniques will provide such an animal as claimed. Applicants have established this extensively in the file history of this application as follows:

> Specification: pages 22-26.
> Additional Evidence: Second Neuhold Declaration, paragraph 9 and Tab 4.

Furthermore, the annexed Askew Declaration (paragraph 11) sets forth that in Dr. Askew's sixteen years of experience in the transgenics field, it would not require undue experimentation to translate success of a transgenic mouse into success of a transgenic rat. In his laboratory, several transgenic mouse models have been successfully translated into rat models. For example, he successfully extrapolated a mouse ALS model to the rat using the exact same transgene used to generate the mouse.

The Examiner has alleged that at the time of filing, the specification was not enabling for non-human transgenic animals because expression of MMP in the joints of an animal would not predictably produce cartilage degradation. The Examiner has argued that the state of the art demonstrated that closely related species carrying the same transgene construct can display widely varying phenotypes. The Examiner has failed to recognize that, at the time of invention, it was known in the art that, as set forth in the specification: (1) both matrix metalloproteinases (MMPs)

and Type II collagen are highly conserved between species; (2) MMPs as recited in the claims degrade Type II collagen; (3) degradation of Type II collagen results in cartilage damage; and (4) generation of transgenic animals was routine. Based upon the highly conserved nature of MMPs and Type II collagen, the known link between Type II collagen degradation and cartilage damage, and the routine nature of generating transgenic animals, it would have been predictable that expression of an MMP in the joints of different species would result in the same phenotype, *i.e.*, cartilage degradation (see Askew Declaration, paragraph 10).

Support for each of these concepts is further set forth in the annexed Askew Declaration.

MMPs Are Highly Conserved Across Species

First, at the time of invention, MMPs were known to be highly conserved across species, and their ability to degrade Type II collagen was known. See Askew Declaration (paragraph 10); specification at page 11, lines 14-21 ("Any polypeptide exhibiting matrix-degrading activity may be used in practicing the invention.... The enzymes may be derived from any animal species"; see also J. Freije, J. Biol. Chem., 269(24):16766-73, 16767 (June 1994) ("Freije") (Exhibit A, which accompanied Response to March 9, 2004 Action); R. Billinghurst, J. Clin. Invest, 99(7):1534-1545, 1534 (April 1997) ("Billinghurst") (Exhibit B, which accompanied Response to March 9, 2004 Action). Freije discloses that as early as 1988, it was known that MMPs showed highly conserved sequence motifs. Freije at 16768. These sequence motifs are highly conserved between mammalian species, and are largely responsible for MMP activity. *Id.*; see also S. Matsumoto, Biochim. Biophys. Acta., 1307(2):137-139 (June 1996) ("Matsumoto") (abstract only) (Exhibit C, which accompanied Response to March 9, 2004 Action); P. Mitchell, J. Clin. Invest., 97(3):761-768, 761 (Feb. 1996) ("Mitchell") (Exhibit D, which accompanied Response to March 9, 2004 Action). Mitchell characterizes MMPs broadly as "vertebrate collagenases," and further discloses that MMPs were known to possess similar activity and function between species. Mitchell at page 761 (homologous rat and human MMPs show similar turnover rate and substrate affinity). Thus, it would be predictable that MMPs expressed in different species, sharing the same or similar highly

conserved sequence motifs, would display the same function and activity, and thus would cleave Type II collagen.

Type II Collagen Is Highly Conserved Across Species

Second, it was well known in the art that Type II collagen is also highly conserved between species. Type II collagen is well known to be found in all multicellular organisms, sharing common structure and properties, and being the form of collagen found in cartilage. See Stryer, Biochemistry, 2d Ed., 185-197, 185 (1975) (Exhibit E, which accompanied Response to March 9, 2004 Action). Type II collagen comprises 90-95% of mammalian articular cartilage, forming fibrils that provide tensile strength and maintain integrity. Billinghurst at 1534 (Exhibit B, which accompanied Response to March 9, 2004 Action). The structure of Type II collagen was known to be "extremely well conserved." M. Vikkula, FEBS Lett. 3; 250(2):171-174 (Jul. 1989) (abstract only) (Exhibit F, which accompanied Response to March 9, 2004 Action); P. Wooley, Crit. Rev. Immunol. 8(1):1-22 (1987) (abstract only) (Exhibit G, which accompanied Response to March 9, 2004 Action). Type II collagen was known to be greater than 80% conserved between mice, rats, chickens, cows, and humans. K. Cheah, Mamm. Genome, 1(3):171-183 (1991) (abstract only) (Exhibit H, which accompanied Response to March 9, 2004 Action). Coupled with the well known conservation of MMP sequence and function, it would be predictable that Type II collagen-specific MMPs would degrade Type II collagen among many different species, since Type II collagen structure is also highly conserved. Thus, contrary to the Examiner's assertions, a species-specific requirement is not necessary, since it would be predictable and expected that MMPs would degrade Type II collagen, regardless of species.

Degradation Of Type II Collagen Results In Cartilage Damage

Third, it was known in the art that degradation of Type II collagen resulted in cartilage damage. Billinghurst discloses that damage to Type II collagen is a critical event in the development of arthritic conditions. Billinghurst at 1534 (Exhibit B, which accompanied Response

to March 9, 2004 Action). Cartilage damage and degradation is a well known characteristic of osteoarthritis, and is known to afflict many vertebrates. A. Hough, Pathology of Osteoarthritis, in Arthritis and Allied Conditions, vol. 2, 1699-1707 (1993) (Exhibit I, which accompanied Response to March 9, 2004 Action). Expression of phenotypes associated with cartilage damage is clearly supported in the specification. See page 18, lines 14-19; page 19, lines 17-23; page 21, lines 4-6. Thus, based upon the state of the art and the disclosure of the present invention, it would have been predictable that degradation of Type II collagen would result in cartilage damage.

The references previously cited by the Examiner allegedly contradict the teaching of the specification. However, the present invention involves expression of enzyme transgenes and degradation of Type II collagen with a high level of sequence, structural, and functional conservation. The Examiner has failed to provide any evidence that the transgenes utilized in the references cited (Ren-2 in Mullins 1990 and Mullins 1989; HLA-B27 in Hammer 1990 and Taurog 1988) have any predictive value of the claimed transgenic mammals that express MMPs. Thus, these references are not indicative of non-enablement of the present invention.

Generation Of Transgenic Animals Is Routine, And Their Phenotype Predictable

Generation of a transgenic animal is routine, and adequately supported by the specification. See page 22, line 15 to page 26, line 8; page 17, line 21 to page 18, line 6. The specification clearly outlines and enables methods for generating particular nucleotide constructs and transforming animals with such constructs. See page 33, line 1 to page 39, line 20. Practicing the disclosed techniques was routine for one skilled in the art, because "... contrary to the examiner's assertions, as of 1996 creation of transgenic mammals required no more than ordinary technical efforts – indeed, technical efforts with shortcomings that are readily overcome." First Neuhold Declaration, paragraph 9. This clear assertion by one of ordinary skill in the art must carry greater weight than the Examiner's characterizations of the cited transgenic animal references. Based upon the disclosure in the specification, generating transgenic animals with similar constructs would be a routine matter for one skilled in the art. Once the transgenic animals are generated, it is a routine matter to screen the animals for expression of the transgene and degradation of collagen.

Once a transgenic animal was generated, and the MMP expressed, it would be a matter of course that cartilage degradation would occur. As discussed above, the high level of sequence conservation in both MMPs and Type II collagen would predictably result in collagen degradation in the transgenic animal, leading to cartilage degradation. Thus, expression of MMPs in the joints of any non-human transgenic animal would predictably produce cartilage degradation, and result in the phenotype of the present invention. Thus, given the disclosure of the specification and the state of the art at the time of invention, a person skilled in the art would have predicted the phenotype generated by expression of MMPs in the joints of a non-human transgenic animal.

The References Previously Cited By The Examiner Support Enablement

The Examiner also cited references (Cameron (1997), Mullins (1990), Hammer (1990), Mullins (1989), Taurog (1988), Mullins (1996), Mullins (1993), Ebert (1988), Wall (1996), and Overbeek (1994)) to support his rejections regarding the alleged lack of enablement of a transgenic mammal. The references cited by the Examiner merely demonstrate that which the skilled artisan in the field of transgenic mammals knows as well as his comrade who generates monoclonal antibodies from hybridomas (or phage display for that matter), or the one who clones individual genes from libraries of cDNAs created from cells or tissues of interest: like most of biology, the process is empirical and involves substantial trial and error, but ultimately, with the proper selection and screening criteria, yields a few successes. In this respect, the process falls well within the parameters set forth in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988) (enablement of broad monoclonal antibody claims despite the larger number of trials necessary to obtain the operative antibody).

Viewed properly, all of the references cited by the Examiner support enablement, because they establish that creating transgenic animals involves routine manipulations and multiple trials to find individuals with the desired genotype and phenotype. As discussed above, inserting the transgene of the present invention into different species of animal would result in the same phenotype, due to the conservation of both MDEs and Type II collagen. In addition to selecting animals with the proper genotype, which the Examiner does not suggest is not enabled, the

specification also sets forth routine screens for the desired phenotype. See page 18, line 22 - page 19, line 2; see also Examples 4-6, page 40, line 1 - page 45, line 7. The conservation of MDEs and Type II collagen, combined with the routine manipulations disclosed by the references cited by the Examiner, establishes that it would be routine and predictable for a person skilled in the art to generate a transgenic animal with the desired phenotype of the present invention.

Cameron discusses the effects of the placement of the transgene with respect to the overall chromatin structure on transgene expression. Nothing in Cameron correlates diversity of chromatin structure with species-specificity. Cameron's description of the effect of placement of the transgene with respect to overall chromatin structure is a relevant issue even within species and is not species dependent. (See p. 256, col. 2, lines 3-9 of Cameron). Cameron describes that such effects are seen with transgenic mice (not between species) made with the same construct. Thus, Cameron supports Applicants' assertion that at the time of the present invention, it was routine for one skilled in the art to screen, whether screening be done within or between species, for transgenic animals that work, *i.e.*, in which transgene insertion occurs at an accessible location in the chromosome. In other words, the requirement to screen and select for a desired transgenic animal is wholly independent of the species selected. Cameron does not correlate genetic diversity or species diversity with unpredictability of transgene expression. Rather, Cameron discloses that all transgene expression depends on random insertion of the transgene in a productive integration site, both within and between species, and that it is routine for one skilled in the art to test and make multiple transgenic animals to find one with the desired phenotype.

The Examiner has also cited Mullins (1993) for teaching that integration of a transgene into a different species of animal results in divergent phenotypes. Mullins (1993) is simply a review article that summarizes references that were already of record (specifically Mullins (1990) and Hammer (1990) (see p. 631, Col. 1, end of ¶ 1 of Mullins (1993)). These references also show that, as with many experimental biological processes, creating a desired transgenic animal requires multiple trials with screening and selection processes to select the successes. The Examiner has failed to establish any reason why the creation of transgenic animals differs from the other biological arts, such as that discussed in *In re Wands*, in this respect.

Mullins (1989) reports success in generating transgenic mice to study tissue-specific expression and control of the Ren-2 gene. Mullins states that expression of the transgene can vary depending on many factors, including the site of integration and the copy number integrated (page 4070). The article shows that even among successfully generated transgenic mice, there is variability in the level of expression. Applicants submit that the potential variability is irrelevant, and that the variable levels of success, or even failure, are a routine part of the generation of transgenic mammals. Indeed, as reported in Example 5 and the First Neuhold Declaration at para. 8, applicants observed variability in expression in the exemplified founder mice.

Taurog (1988) reports success introducing the MHC Class I antigen HLA-B27 into both inbred and hybrid mice, for use in studying the role of HLA-B27 in inflammatory human disease. In order to generate the transgenic mice, over 600 embryos were fertilized, with less than 1/6 of these embryos generating live pups (see page 4021-4022). An even smaller fraction expressed HLA-B27 in significant amounts (see Id.). Applicant submits this reference shows that although the number of failures is large, it is routine for such failures to occur, and that the failures are irrelevant in light of the eventual success. Nothing in Taurog suggests that screening and selecting of the successes required other than routine experimentation.

Mullins (1996) reports that transgenic technology, including embryonal stem (ES) technology, was well established at the time of invention (page S37). Time and cost, issues irrelevant to enablement, limit the desirability of pronuclear injection in larger mammals. Mullins 1996 at page S37. No matter, as pointed out in the specification, ES technology is an alternative. See page 25, line 1 - page 26, line 8. Pronuclear injection also provides for transgene insertion. See page 23, line 13 - page 24, line 3. The fact that pronuclear injection is less efficient, and therefore economically undesirable, does not establish that it does not work. On the contrary, nothing in Mullins (1996) supports such a conclusion. In any event, this paper reports a number of successful non-murine transgenic animal models (see page S38).

Ebert (1988) reports success generating experimental transgenic animals for disease models ("Transgenic pigs carrying this fusion gene had elevated levels of circulating human somatotropin"; see page 277). Applicants submit that the presence of failures is irrelevant in the face of success;

the entire history of modern molecular and cellular biology is one of selecting and screening for successes from the much more abundant failures, as demonstrated in *In re Wands*.

Wall reports that 6000 papers describe transgenic animals, mostly mice, to answer research questions (pages 58, 60, and 61). Wall states that "genes can... be modified to function very differently than they do in their native form (gene products, tissue specificity, and timing of expression can be altered)" (page 58). In other words, Wall specifically states that the features of Applicants' invention can be achieved. Wall does concede that transgenic farm animals are costly (mostly because it takes many attempts to yield the desired transgenic animal) (see page 6), however, economic issues are irrelevant to enablement. How is it possible that a reference acknowledging such an abundance of research papers on transgenic animals, manipulation of expression, and at least 1% efficiency of obtaining the desired transgenic animal (much higher, one might add, than the likelihood of obtaining a desired monoclonal antibody or even cloning a gene) calls into question enablement of this invention? On the contrary, Applicants submit such a reference supports the routine nature of generating experimental transgenic animals for disease models.

Overbeek shows that different transgenic animals within a single species will demonstrate different levels of expression. Regulatory sequences help avoid variability (see page 97) but this makes little difference: variability ranges from one extreme to another, from no phenotypic change to the desired change. This establishes predictability of two things: there will be failures, and there will also be successes. By selecting the successes, which is routine, one obtains the desired transgenic animals. Indeed, applicants themselves had failures, however, successful animals were obtained (see specification at page 43).

For these reasons, and the reasons previously made of record, none of the references cited by the Examiner establish lack of enablement with respect to the claimed "transgenic non-human mammals." Such animals are enabled; given the tools (in this case the MDE, regulated expression system, and tissue-specific expression system) and the mechanisms for testing (any of the indicia of collagen II degradation), it is merely routine experimentation to make and test transgenic animals to find one that works. As pointed out above, making a transgenic animal involves the same empirical

testing process as making any other biotechnological material. In *In re Wands* the courts have acknowledged that in the field of biology, a lot of experimentation can be necessary and that most attempts to achieve the experimental goal will result in failure, but that as long as one can screen for successful results, such experimentation does not constitute undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404. For example, in *In re Wands*, the court found the following process did not constitute undue experimentation:

> by screening enough clones (often hundreds at a time), hybridomas may be found that secrete antibodies against the antigen of interest. 858 F.2d at 738

The Examiner also alleges that several animal models of disease have relied on transgenic rats when the development of mouse models was not feasible, and argues that closely related species carrying the same transgene can exhibit widely varying phenotypes. The Examiner alleges that Mullins 1989 and Mullins 1990 show, respectively, the failure to generate a transgenic, hypertensive mouse expressing Ren-2, followed by successful generation of a transgenic, hypertensive rat. However, unlike the phenotype of the present invention, "the mechanism responsible for elevating blood pressure remains to be established." Mullin 1990 at page 543. Thus, other, unknown factors may be responsible for the generation of the hypertensive phenotype in rats, and may cause the difference in results observed in Mullins 1989 and Mullins 1990. In contrast, the mechanism for cartilage degradation in accordance with the claimed invention is known, e.g., Type II collagen degradation by MDEs. In combination with the fact that the elements of the mechanism of cartilage degradation are highly conserved, it is therefore possible to predict the phenotype of a transgenic animal expressing the transgene of the present invention. See page 11, lines 14-21, and Freije at 16767.

Similarly, the Examiner argues that Taurog 1988 and Hammer 1990 respectively show the failure to generate a HLA-B27 transgenic mouse with an inflammatory disease phenotype, followed by successful generation of a transgenic rat. However, the HLA-B27-associated disorders comprise a large group of heterogeneous disorders, and the common pathogenic mechanism underlying these disorders is unknown. Thus, the unpredictable results observed in Taurog 1988 and Hammer 1990 are most likely due to the lack of knowledge regarding the underlying disease mechanisms. These

references cannot be used to establish unpredictability of the phenotype of the present invention, because the pathogenic mechanism for cartilage degradation in the invention is known and the elements of the mechanism are highly conserved. See page 11, lines 14-21, and Freije at 16767. Therefore the phenotype of a transgenic animal of the present invention is predictable.

Finally, the Examiner cites references from almost a decade before the application filing date, namely, Mullins (1990), Hammer (1990), Mullins (1989), Taurog (1988), Mullins (1993), and Ebert (1988). Such dated references cannot constitute the state of the art, because "[e]nablement is determined from the viewpoint of persons of skill in the field of the invention at *the time the patent application was filed.*" *Ajinomoto Co., Inc. v. Archer DanielsMidland Co.*, 228 F.3d 1338, 1345, 56 USPQ2d 1332, 1337 (Fed. Cir. 2000) (emphasis added). To establish the viewpoint of persons of skill in the field on the basis of references over ten years prior to the time the application was filed ignores technical advances that occur between the time the reference was published and the time the application was filed. A difference of over ten years is enough that "in view of the rapid advances in science... what may be unpredictable at one point in time may become predictable at a later time." *Enzo Biochem, Inc. v. Calgene, Inc.*, 188 F.3d 1362, 1374, footnote 10, 52 USPQ2d 1129, 1138, footnote 10 (Fed. Cir. 1999).

In sum, non-human mammals, such as the presently claimed rats and mice, are enabled by the specification.

<u>Rejections under 35 U.S.C. § 112, second paragraph</u>

The Examiner rejected claims 90-96 under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularity point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Examiner contends that step (a) of claims 90-96 as previously presented is not clear because it does not require that the mammals have "a loss of proteoglycan, cleavage of type II collagen into a TCA degradation product..." as in the preamble of the claims. In response to this rejection, claims 90-96 (specifically, new step (b) of these claims) have been amended to specify the specific phenotypes (*i.e.*, those recited in the preamble). Accordingly, Applicants respectfully request withdrawal of this rejection.

In addition, the Examiner alleges that there appears to be a separate step in the phrase of "activating" MMP expression in the first and second mammal. Claims 90-96 have been amended to add step (b), which expressly recites "activating expression of the metalloproteinase…" Accordingly, Applicants respectfully request withdrawal of this rejection.

Lastly, the Examiner alleges that there is no antecedent basis for the phrase "phenotypic change" in the last "wherein" clause of claims 90-96. In response to this rejection, the phrase "phenotypic change" has been replaced with the term "phenotype," which has proper antecedent basis. Accordingly, Applicants respectfully request withdrawal of this rejection.

It is believed that the indefiniteness rejections have been obviated and Applicants respectfully request withdrawal of these rejections.

CONCLUSION

In view of the above amendments and remarks, it is respectfully requested that the application be reconsidered and that all pending claims be allowed and the case passed to issue. If there are any other issues remaining which the Examiner believes could be resolved through a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

Dated: September 2, 2005

Respectfully submitted,

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